Glomerular filtration rate in type 1 diabetic adolescent by using single plasma sample and gamma camera methods

GFR in type 1 DM by using single plasma sample

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Abstract

Aim: Type-1 diabetes mellitus (DM) has indicated that glomerular hyperfiltration (GFR) is a risk factor for nephropathy. Renal pathological changes develop before features of clinical renal disease including proteinuria and declining GFR are evident. We investigated changes in GFR in children and adolescents with type 1 DM by means of single plasma sample (SPS) and gamma camera Gate's methods using Tc-99m DTPA. Additionally, we determined the specificity, sensitivity, and consistency of the two methods.

Material and Methods: Thirty-six patients (mean age: 15.01±4.03 years) with Type-1 DM (19 males, 17 females) were studied. Impairment of renal function was not detected in any of the patients with routine biochemical tests. Standard Tc-99m DTPA renal images were obtained for 40 minutes and GFR is calculated by Gate's method and values>130/1.73m2 b.s. were considered hyperfiltration. SPS was obtained at 120 min-post injection and the Cristensen-Groth equation (CG) was used. The patients were divided into two groups according to the duration of diabetes as less than 5 years (Group A) and longer than 5 years (Group B).

Results: In Group A, hyperfiltration was detected in 11 of 14 patients with SPS, whereas in 7 of 14 patients with Gate's method. In Group B, hyperfiltration was detected in 17 of 22 patients with SPS, whereas in 13 of 22 patients with Gate's method. Sensitivity of Gate's method was 67.9 % in all patients for diagnosis (Sensitivity: 67.9%, Specificity: 87.5 %, positive predictive value (PPV): 95 %, negative predictive value (NPV): 43.8%). The consistency of these two methods was found as 72.6% (p=0.005).

Discussion: Gate's method is useful for clinical practice due to ease of use and high consistency with SPS, especially in the children. SPS remains the first-line method of GFR measurement in suspected diabetic nephropathy patients.

Keywords

Type-1 diabetes; Glomerular filtration; Gamma camera; Tc-99m DTPA; Single plasma

Introduction

Diabetes is a complete or partial deficiency of insulin secretion or carbohydrate, protein, and fat metabolism disorder caused by a different degree of insulin resistance. Prognosis in diabetic patients is closely related to degenerative complications. Microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (atherosclerosis) complications occur 10 to 15 years after the onset of diabetes [1]. Diabetic nephropathy is rare in the child age group. It is proteinuria as the first symptom, usually 10 years after the onset of diabetes. Proteinuria, which does not show any clinical symptoms initially, is accompanied by edema, hypertension, and progressive impairment in kidney function. Nodular glomerular sclerosis and diffuse intracapillary glomerular sclerosis are detected in histopathology of the kidney. There is a thickening of the basement membrane in electron microscopy [2]. Diabetic nephropathy is the cause of death in 50% of patients with juvenile diabetes. Diabetic nephropathy encompasses a variety of kidney lesions such as diabetic glomerulosclerosis, arteriolosclerosis, increased sensitivity to pyelonephritis, and papilla necrosis [3].

Type 1 diabetes mellitus (DM) have indicated that glomerular hyperfiltration is a risk factor for diabetic nephropathy. In the early stages of DM, the renal plasma flow and the glomerular filtration rate (GFR) have often been found higher than normal. Hyperfiltration occurs in the early stages of DM and has been implicated development of microalbuminuria. In diabetic rats increased GFR, in association with elevated intraglomerular pressure was positively related to subsequent glomerulosclerosis [4, 5].

Renal dynamic imaging with 99mTc-diethylene triamine pentaacetic acid (99mTc-DTPA) is a commonly used method to determine renal blood flow and unilateral kidney function. The timed uptake curves of the two kidneys, especially the comparison, give notable information such as quantitative unilateral renal function and pathophysiological changes in the kidney in renovascular hypertension, hydronephrosis, and renal transplant [6, 7]. Since it is exhaustive and difficult to perform in routine clinical practice, single plasma sample (SPS) method and double plasma sample method of GFR estimation were derived from the multi-sample technique. Multi, double, and single-sample techniques were observed to have a significant correlation [8]. Apart from the plasma sample technique, few computer-based methods have also been developed among which the gamma camera (GC)-based method became highly popular as it can provide an immediate calculation of individual kidney function as well as of global renal function. The most popular calculation method nowadays is the modified Gate's method, which is commercially available. To measure glomerular filtration rate (GFR) using this kind of gamma camera method, no blood and urine collection is needed, and measurement takes approximately only 20 min. Because of its convenience, it is usually used as a surrogate of GFR in some clinical trials [9].

Renal pathological changes develop before features of clinical renal disease including proteinuria and declining GFR, become evident. We investigated changes in glomerular filtration rate in children and adolescents with type 1 DM by means of single plasma sample (SPS) and gamma camera methods using Tc99m-DTPA.

Material and Methods

The research study was approved by the Celal Bayar University Health Sciences Ethics Committee. Written informed consent was obtained from all participants of the study. Thirty-six patients (mean age: 15.01 ± 4.03 years) with type 1 DM (19 males, 17 females) with the duration of diabetes between 3 months to 18 years (mean: 6.48 ± 3.8 years) were studied. Impairment of renal function was not detected in any of the patients with routine biochemical tests. The patients were divided into two groups according to the duration of diabetes as less than 5 years (Group A) and longer than 5 years (Group B). All subjects were hydrated with 500 ml of fluid 30 minutes prior to the test. The patients were asked to void before Tc99m DTPA injection. The patient lay down on a bed in the supine position. Following immediately intravenous injection of Tc99m-DTPA (AmerscanTM Pentetate II Agent) about 200μCi/kg through an indwelling butterfly needle in an antecubital vein, acquisition with gamma camera (General Electric, 600 XR/T, Rectangular) which was attached to a low energy general-purpose parallel hole collimator started and renal images were obtained for 40 minutes. Frames of 64 x 64 matrix were recorded with an online-computer, initially at one second for one minute and then at 60 seconds for 39 minutes. The percent renal uptake at 2-3 min after tracer arrival in the kidney was determined with background subtraction. The GFRGates was automatically estimated by a commercially available computer (Entegra, GE) according to the Gates' algorithm. A standard solution (diluted) was prepared. The blood samples were taken 120 minutes after injection of radiotracer and plasma samples were obtained from that blood samples. After both 1 ml standard solution and 1 ml plasma sample were counted in the well counter (Biodex Medical System; Atomlab 950). The GFRsps was determined from a single-plasma concentration at 120 minute-post-injection using Christensen-Groth's equation. Christensen and Groth introduced another one-compartment method by estimating extracellular volume from the body surface area. The GFR (ml/min) obtained by the two methods was normalized for a body surface area of 1.73 m2 according to Haycock's equation and values>130 were considered hyperfiltration.

Statistical analysis

The data were analyzed using SPSS 25.0 statistics program. The paired Mann-Whitney-U test, Fisher's exact test, Pearson correlation, and Kappa consistency analysis were used for statistical analysis. Values smaller than p <0.05 were considered statistically significant.

Results

The anthropometric properties and clinically obtained metabolic data of the research population are shown in Table 1. The average age of the patients was 15.01 ± 4.03 years, BSA mean 1.46 ± 0.31, DM diagnosis time 6.48 ± 3.8 years, insulin dose (U / kg) mean 45.19 ± 14.91 and HbA1c mean (%) was 11.0 ± 0.03 (Table 1).

GFR values of the research population obtained by scintigraphically single plasma sampling and gamma camera methods are shown in Table 2. The normalized GFR mean measured by Gate's gamma camera method was 148.27 ± 51.84, whereas GFR mean measured by the Single plasma

sampling method was 177.53 ± 38.00 (Table 2).

GFR value of 130 ml/dk/ m2 cut point is taken and the comparison of GFRs calculated by single plasma sampling and normalized gamma camera method is shown in Table 3. Assuming a hyperfiltration limit of 130 ml/min/ m2 and above, glomerular hyperfiltration was detected in 28 (78%) of 36 patients with GFRs calculated by a single plasma sampling method. Considering the normalized GFR values in Gate's gamma camera method, glomerular hyperfiltration was detected in 20 (56%) of 36 patients (Table 3).

In comparison of GFR values and Type 1 DM diagnosis time distributions of the two groups, the number of patients with Type 1 DM for less than 5 years was 14 (39%), the number of patients with Type 1 DM for more than 5 years was 22 (61%). GFRsps values (196.9 ± 92.6) are statistically significant higher than GFRgate's values (139.6 ±57.9) in the Type 1 DM for less than 5 years group (p=0.017). In comparison of GFR values measured according to diabetes duration, in Group A, hyperfiltration was detected in 11 of 14 patients with SPS, whereas in 7 of 14 patients with Gate's method. In Group B, hyperfiltration was detected in 17 of 22 patients with SPS, and in 13 of 22 patients with Gate's method. Sensitivity of Gate's method was 67.9 % in all patients for diagnosis (Sensitivity: 67.9 %, Specificity: 87.5 %, positive predictive value (PPV): 95 %, negative predictive value (NPV): 43.8%). The consistency of these two methods was 72.6 % (p= 0.005). In comparison of Pearson's correlation between insulin doses and BSAGFR and NORMGFR, there was a statistically significant negative correlation between insulin doses and BSAGFR and NORMGFR (r: -0.543 **, p = 0.001 and r: -0.461 **, p = 0.005, respectively). The relationship of GFR values normalized to the body surface area obtained from two separate plasma samples prepared from the patients' plasma at the same time is shown in Figure 1. To evaluate their accuracy, two plasma samples of 1 ml were obtained from each patient. As a result, the correlation coefficient between GFR amounts calculated from both single plasma samples, corrected for body surface area, was found to be r: 0.833 and p = 0.001, and a linear curve was obtained (Figure 1A).

When compared to the single plasma sampling method and the gamma camera method (Gate's), which showed the distribution volume at the 2nd hour in 36 patients included in the study and whose Type 1 DM diagnosis period ranged from 3 months to 18 years, the consistency between the two methods was 66.7% (kappa: 0.314 and p: 0.034) (Figure 1B).

The comparison of body surface area (BSA) and normalized GFR values calculated with Gate's method is shown in Figure 3. As the body surface area of the patient increases, the normalized GFR value decreases as calculated by the Gate's method. Since the surface area increases, the attenuation factor also increases and the GFR value is calculated below the predicted (Rho = - 0.733, p = 0.001) (Figure 1C).

In addition to the gamma camera method, there was also information we obtained which allowed us to have information about kidney function individually. Although the blood urea and creatinine levels of the patients participating in the study were within normal limits, seven of the patients had normal kidneys while the other had nonobstructive dilatation. We found renal

dysfunction in four of them, nonobstructive dilatation in both kidneys and in one patient, obstructive in one kidney, and in nonobstructive dilatation patterns in the other.

Table 1. The anthropometric properties and clinically obtained metabolic data of the research population

	Mean ± SD	Median
Gender (K / E)	17 / 19	
Age (years)	15.01 ± 4.03	15.50
Height (cm)	156.50 ± 19.67	160
Weight (kg)	49.50 ± 15.20	51.00
BSA (m2)	1.46 ± 0.31	1.52
Adapted to body surface area		
LBM (kg)	39.71 ± 10.11	41.20
Adapted to body lean mass		
DM diagnosis time (years)	6.48 ± 3.8	6.00
Insulin dose (U / kg)	45.19 ± 14.91	47.00
HbA1c (%) n = 25	11.0 ± 0.03	11.0
Urine microalbumin (µg/dk) n = 25	20.57 ± 9.68	20.00

Table 2. GFR values of the research population obtained scintigraphically with single-plasma sampling and gamma camera methods

GFR calculation methods	Mean ± SD	Median
Gate's gamma camera method Normalized GFR (ml/dk/m 2)	148.27 ± 51.84	135.65
Single plasma sampling method GFR (ml/dk/1.73 m²)	177.53 ± 38.00	153

Table 3. GFR value of 130 ml/min/ m2 cut point is taken and the comparison of GFRs calculated with single plasma sampling and normalized gamma camera method (Fisher's exact test, p=0.050)

			NORMGFR		Total
			<130 ml/min/m2	>130 ml/min/m2	
BSAGFR	<130 ml/min/m2	n	6	2	8
		BSAGFR%	77.8%	22.2%	100%
		NORMGFR%	41.2%	10.5%	25.0%
	>130 ml/min/m2	n	10	18	28
		BSAGFR%	37.0%	63.0%	100%
		NORMGFR%	58.8%	89.5%	75.0%
Total		n	17	20	36
		BSAGFR%	47.2%	52.8%	100%
		NORMGFR%	100%	100%	100%

BSAGFR: Glomerular Filtration Rate based on body surface area.
NORMGFR: Glomerular Filtration Rate calculated by normalized gamma camera method.

Discussion

In our study, it was found that compared to normalized GFR measurement calculated by Gate's method, BSAGFR measurement obtained with a single plasma sampling method and corrected by body surface area correction showed kidney function more accurately in patients with Type 1 diabetes
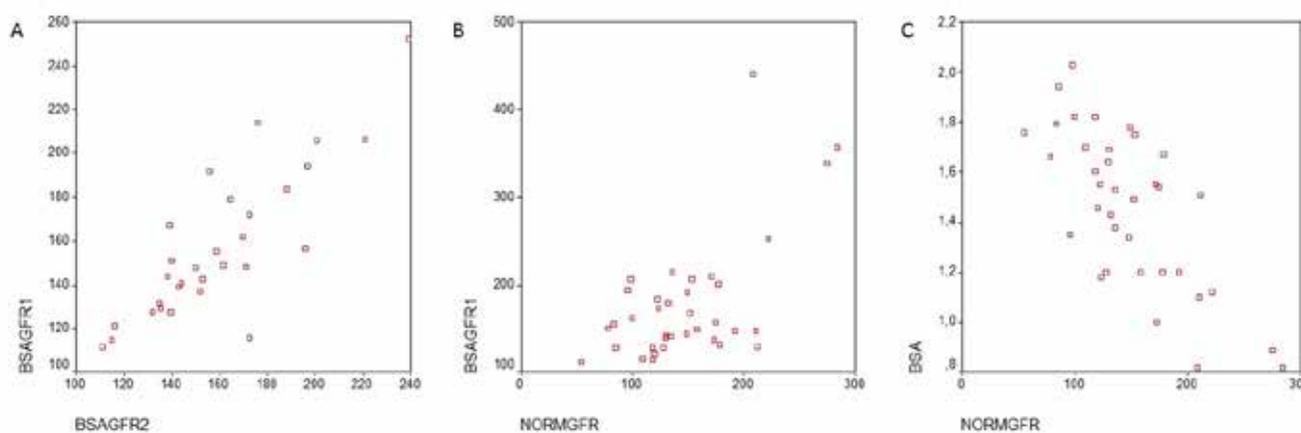
Figure 1. A. The relationship of GFR values normalized to the body surface area obtained from two separate plasma samples prepared from the patients' plasma at the same time (Rho = 0.833, p = 0.001). B. Consistency between single plasma sampling method and Gate's gamma camera method (Rho = 0.615, p = 0.001). C. The comparison of body surface area (BSA) and normalized GFR values calculated with Gate's method.

mellitus. However, there was a statistically significant negative correlation between the insulin doses and BSAGFR and NORMGFR (r: -0.543**, p=0.001 ve r: -0.461**, p=0.005, respectively). It was found that BSAGFR value correlated better with insulin doses compared to NORMGFR.

Failure to detect individual kidney GFR rapidly or evaluating the correct GFR in varying situations are seriously limiting the use of creatinine clearance. Radionuclide techniques have evolved to overcome these limitations and meet the needs of evaluating renal functions in clinical trials. In general, after meeting ERPF-based renography in clinical studies, radionuclide techniques used to measure GFR have been developed [10]. The chemical properties of inulin do not allow for easy binding with radioactive isotopes, however C-14, I-125, I-131 and Cr-51 have been used for GFR measurement, although the degree of success varies [11]. After the development of the gamma camera and the use of Tc-99m bound kidney screening agents, new horizons have been opened clinically for radionuclide renography. Technetium-99m-pertechnetate was used with a gamma camera in the dynamic renal scintigraphy study to evaluate the vascularity of kidney lesions [12]. The DTPA technique associated with Technetium-99m is still an excellent radiopharmaceutical that can calculate the GFR measurement while performing a radionuclide renogram [13]. Tc-99m-DTPA allows imaging of the kidneys using a gamma camera. The distribution of function between the kidneys on both sides depends on the amount reaching the kidneys in a short time following radiopharmaceutical application [13]. Tc-99m-DTPA has ground-corrected relative renal uptake. This fractional distribution of activity is determined by image analysis and is then used to calculate the percentage distribution of each kidney with total GFR. The last value of the two (total GFR) can be determined using either single or multiple blood sampling or gamma camera techniques. The relative distribution of activity between the kidneys occurs within 2 to 3 minutes following the arrival of the radiopharmaceutical. It is stated that the best time for determining the relative distribution of the function between the kidneys is 2-3 minutes when Tc-99m-DTPA is used,

while the others are used for 1-3 minutes [14]. In our study, Normalized GFR measured by Gate's gamma camera method using by Tc-99m-DTPA was 148.27 ± 51.84.

In 1975, Fisher and Veall predicted GFR with a modified single blood sampling technique [15]. Bibbo et al. reported a very good correlation between the two methods in the study comparing single injection, single plasma sample diatrizoate and Inulin clearance in detecting GFR [16]. Nautiyal et al. reported that Gates method of GFR estimation using a Gamma camera shows a significant correlation with plasma sample technique in people with normal BMI. In people with BMI outside the normal range, it significantly underestimates GFR [17]. In the GFR estimation, Ham and Piepsz showed that there was a linear equation suitable for children of all ages by linear regression equation converting the 2nd hour distribution volume data [18]. However, they recommended the use of a single sampling technique for GFR measurement in Children. In our study, we have seen that the plasma sampling method gives more accurate results about GFR than the gamma camera method as stated in the literature. However, considering the difficulty of taking blood from young patients and the depth of the kidney is less, we can estimate GFR with the gamma camera method. Glomerular hyperfiltration has also been reported as a risk factor for type 1 DM in diabetic nephropathy [19, 20]. Gao F and Zhang C have found glomerular filtration in diabetics for less than 5 years in diabetic mellitus (NIDDM) in patients with diabetes mellitus (NIDDM) in their studies evaluating radionuclide renal dynamic imaging in the diagnosis of diabetic nephropathy. In diabetics, this situation has deteriorated for more than 5 years [21]. However, they found it particularly supportive in the early diagnosis of glomerular hyperfiltration, especially diabetic nephropathy, without nucleic renal dynamic imaging β2-microglobulinuria and microalbuminuria [21]. Itoh reported that the single sampling method was more accurate than the gamma camera method and the gamma camera method was more accurate than the 24-hour creatinine clearance in predicting studies with the single sampling and gamma camera methods for detecting GFR with Tc-99m DTPA.

It should be kept in mind that the only sampling method is more accurate in detecting GFR and DTPA in a patient with moderate and moderate renal dysfunction [22]. Itoh et al reported that the only sampling method was the first choice in a routine application due to its technical simplicity and accuracy in the study where they investigated the accuracy of the single sampling method for detecting GFR with Tc-99m DTPA [23]. In our study, when over 130 ml / min / m2 was considered as hyperfiltration, hyperfiltration was detected in 78% of patients in the single plasma sampling method (body surface area correction) taken at 120 min, and 56% in the gamma camera method (Gate's). At this stage, patients are recommended to reduce the amount of protein in the diet.

Conclusion

Our study shows that reliable estimation of absolute GFR is possible from the routine dynamic renal scinti-scanning procedure using the gamma camera computer systems, and hence might prove applicable in clinical practice. Although the Gate's method requires neither blood sampling nor additional imaging, the plasma sampling method could be used as a first choice in detecting GFR in patients suspected of diabetic nephropathy, as we want to calculate the GFR more accurately.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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